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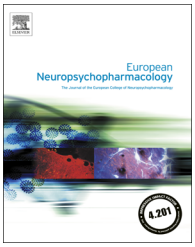

Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests

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Abstract
The cumulative duration of depressive episodes, and their repetition, has a detrimental effect on depression recurrence rates and the chances of antidepressant response, and even increases the risk of dementia, raising the possibility that depressive episodes could be neurotoxic. Psychomotor retardation could constitute a marker of this negative burden of past depressive episodes, with conflicting findings according to the use of clinical versus cognitive assessments. We assessed the role of the Retardation Depressive Scale (filled in by the clinician) and the time required to perform the neurocognitive d2 attention test and the Trail Making Test (performed by patients) in a sample of 2048 depressed outpatients, before and after 6 to 8 weeks of treatment with agomelatine. From this sample, 1140 patients performed the TMT-A and -B, and 508 performed the d2 test, at baseline and after treatment. At baseline, we found that with more past depressive episodes patients had more severe clinical level of psychomotor retardation, and that they needed more time to perform both d2 and TMT. When the analyses were performed again after treatment, and especially when the analyses were restricted to patients with clinical remission, the cognitive tests were the only ones correlated with past depressive episodes. Psychomotor retardation tested at a cognitive level was therefore systematically revealing the burden of past depressive episodes, with an increased weight for patients with less remaining symptoms. If prospectively confirmed, interventions such as cognitive remediation therapy could benefit from a more specific focus on neurocognitive retardation.

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1. Introduction

The cumulative duration of depressive episodes, as well as their repetition, has a detrimental effect on depression recurrence rates (Solomon et al., 1997), the chances of antidepressant response (Keller et al., 1992), time to obtain remission (Kanai et al., 2003), and the presence of social recovery (Sarapas et al., 2013). Memory impairment (Burt et al., 1995), atrophy of the hippocampus (Sheline et al., 1999), and higher risk for dementia (Kessing, 2012) have also been observed, raising the possibility that depressive episodes could be neurotoxic (Gorwood et al., 2008).

Some neurocognitive deficits may constitute a core feature of major depressive disorder (MDD), as they have also been observed during clinical remission (Austin et al., 2001; Bhardwaj et al., 2010; Weiland-Fiedler et al., 2004) and predict a higher degree of follow-up symptoms over and above the initial symptoms (Sumner et al., 2010). The cognitive functions involved concern reduced memory capacity (Gorwood et al., 2008), decreased flexibility and psychomotor speed (Beats et al., 1996; Austin et al., 2001), attention and set-shifting deficits (Purcell et al., 1997; Austin et al., 2001), reduced vigilance, and psychomotor slowness (Den Hartog et al., 2003; Egeland et al., 2003; Arnett et al., 1994; Kertzman et al., 2010). The fact that Attention Deficit-Hyperactivity Disorder symptom severity was significantly correlated with the occurrence of lifetime depressive episodes, even after controlling for current comorbidity (Simon et al., 2013), might also plead in favor of a tight relationship between attention processes and major depressive disorder.

Psychomotor retardation could be involved more specifically. Not only is this considered a core clinical feature of depression by many clinicians (Widlocher, 1983), but it is also a neurocognitive trait frequently assessed in mood disorders. For example, the presence of 'marked psychomotor retardation' is included among the symptom criteria required for a diagnosis of a depressive episode in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and has proven to have both diagnostic and prognostic value in major depression (Calugi et al., 2011). Psychomotor retardation can also be easily assessed as a cognitive trait through the use of simple drawing tasks (Sabbe et al., 1999; Buyukdura et al., 2011), which have the advantage of being independent from clinical assessments, the latter being frequently contaminated by the severity of depressive symptoms. High levels of psychomotor retardation have indeed been observed in depressed patients using a variety of paradigms, even in patients who are in remission (Beats et al., 1996; Austin et al., 2001; Den Hartog et al., 2003; Egeland et al., 2003; Arnett et al., 1994; Kertzman et al., 2010; Hasselbalch et al., 2013).

The link between psychomotor retardation in depressive disorder and cognitive impairment remaining after depressive disorder needs to be highlighted because of the therapeutic strategies that could be involved. Actually, clinical psychomotor retardation, unlike the intensity of a depressive episode, appears to correlate with a decrease in performance level on attentive tasks, which attests to the specific value of clinical psychomotor retardation as a predictor of cognitive deficits in depressed patients (Lemelin and Baruch, 1998). Furthermore, in a study in patients with remitted MDD, the deficit in psychomotor speed remained significant, suggesting that it constitutes a vulnerability marker for, or stigma of, MDD (Weiland-Fiedler et al., 2004).

Two tests are of significant interest when assessing psychomotor retardation as well as attentive and set-shifting processes. One of these is a Trail Making Test (TMT A & B), a frequently-used neurocognitive drawing test that can measure psychomotor retardation (Buyukdura et al., 2011; Partington, 1949), especially when the interest is in speed rather than number of mistakes. The other is the d2 test of attention, a graphic-motor test of cancellation aimed at assessing basic attention level (Brickenkamp, 1981) through the number of correct items quoted by the patient within a limited amount of time. As the three tests (d2 test, TMT-A, and TMT-B) all rely on speed, they are good indicators of psychomotor retardation. However, these tests vary in terms of their level of demand and thus have variable sensitivity for psychomotor retardation: the d2 test (theoretically) is limited to the attention process, while TMT-A also involves a motor task (drawing adequate lines) and TMT-B, besides these aspects, also requires set-shifting skills.

The majority of studies, but not all, report beneficial effects of antidepressants in improving different neurocognitive functions (i.e., executive function, memory, and/or attention skills) in depressed patients (for example Herrera-Guzman et al., 2009), including psychomotor retardation. We focused on agomelatine because of its activity in relation to circadian rhythms, which are an important aspect of psychomotor retardation (Moffoot et al., 1994; Sabbe et al., 1999). The other reason for our focus on agomelatine was its activity in relation to dopamine neurotransmission (Chenu et al., 2013), a key player in psychomotor retardation (Rampello et al., 1991).

In order to more precisely define which stigmas characterize patients with past depressive episodes, we analyzed the level of psychomotor retardation in depressed patients and tested the hypothesis that it would reflect the number of past depressive episodes, even when patients are in clinical remission. Furthermore, we also tested whether a simple cognitive drawing test (TMT and/or d2 tests) could be more informative in determining past depressive episodes than a specific scale assessing clinical psychomotor retardation (the retardation depressive scale [RDS]). To test this hypothesis, we analyzed different aspects of psychomotor retardation using data from an original, large, prospective and non-interventional study of agomelatine in the treatment of depressed outpatients, which included neurocognitive tests in a subsample of patients assessed before and after treatment.

2. Experimental procedures

The present multicentre, non-interventional study was conducted in a naturalistic treatment setting in 388 community psychiatry centres in France between October 2011 and October 2012. A total of 2048 outpatients (Table 1) were initially recruited, all of whom fulfilled the DSM-IV criteria for major depressive disorder and required (according to the clinician) the prescription of one (and only one) antidepressant treatment. Exclusion criteria were being aged under 18 years, having a psychotic manifestation, an

Table 1 Demographic and clinical characteristics of 2048 depressed outpatients at baseline.

Characteristics	Subgroups	Baseline values			
		N	%	Average	SD
Gender	Female	1290	63.14		
	Male	753	36.86		
Age (years)				45.38	12.27
Marital status	Single, divorced, or widowed	1061	53.08		
	Married/partner	938	46.92		
Highest educational level	Below high school	1094	55.62		
	High school and over	873	44.38		
Professional activity	Presently working	811	43.37		
	Retired, unemployed, disability, or sick leave	1059	56.63		
Length of present episode (weeks)				9.90	25.98
Number of past episodes				0.91	1.66
	0 (first episode)	1207	61.64		
	1	276	14.10		
	2	203	10.37		
	3	128	6.54		
	4 and more	144	7.35		

SD; standard deviation.

associated axis I psychiatric illness, a severe or unstable medical condition (i.e., hepatic insufficiency), a current diagnosis of substance abuse (drug or alcohol), pregnancy or lactation, antipsychotic and benzodiazepine treatment, and administration of electroconvulsive therapy in the preceding 6 months. Patients were assessed twice – once at baseline (before treatment) and once after 6 to 8 weeks of medication. The average delay before this second visit was 50 days (standard deviation [SD]=11 days). As we did not find any impact of this delay on the clinical and cognitive characteristics of patients at the second visit, this parameter was not controlled for.

The study was approved by the French National Ethics Committee and all patients gave written informed consent prior to participation. All data were recorded anonymously.

2.1. Clinical assessments

A number of socio-demographic characteristics were assessed (Table 1), and these were simplified in the statistical analyses to focus on the most informative aspects. Accordingly, the level of education was analyzed as being below or above high school level, marital status as living or not with a partner, and professional activity as being presently active or not (Table 1).

The diagnostic of major depressive episode was based on (1) clinician diagnosis (as the decision to 'prescribe an antidepressant to treat a major depressive episode' was the inclusion criteria), (2) a specific assessment of the nine DSM-IV criteria for major depressive episode (and the fact that at least 5 of these criteria are present) and the (3) Self-Report Quick Inventory of Depressive Symptomatology (QIDS-SR). This 16-item brief rating of depressive symptoms was designed to assess severity, but has highly acceptable psychometric properties and usefulness (Rush et al., 2003) and good capacity to correctly classify depressed patients in primary care centres (Lamoureux et al., 2010).

The threshold for clinical remission was defined as a QIDS-SR score of ≤ 5 (Rush et al., 2003).

The Widlöcher RDS is a 15-item scale filled in by a clinician. It assesses cognitive and motor aspects of psychomotor retardation (Widlocher, 1983).

The Sheehan Disability Scale (SDS) is a brief self-report tool that assesses functional impairment in three related domains: work/school, social, and family life. The patients rate the extent to which their responsibilities in each domain are impaired by their symptoms on a 10-point visual analog scale (Leon et al., 1992).

2.2. Cognitive tasks

The d2 test was completed first, followed by TMT-A and TMT-B. The d2 test of attention is a graphic-motor test of cancellation aimed at assessing attention (Brickenkamp, 1981). The test includes a task involving the cancellation of specific designated letters (*p* or *d*) with small vertical lines above and/or below the letters. The test has 14 rows of 47 characters in each row – a total of 658 characters. Participants are allowed 20 s to cancel the designated letter (the letter *d*) on each row, with 2 small vertical lines below and/or above the letter. The task lasts for 4 min and 40 s. Before starting the test in our study, each participant was given a full explanation and practiced the task in a one-line trial. The test assessed attention through the rate of cancellation, accuracy, consistency of the work, and the number of mistakes. Generated variables mainly include total signs marked (GZ, quantitative performance index), total signs correctly marked (BR), and total signs correctly marked minus incorrect marked items (KL, concentration performance index). Qualities of the test include a test-retest reliability of >0.90 in numerous studies (Antretter et al., 2013).

The TMT (Partington, 1949) is a commonly-used neuropsychological drawing test that can measure psychomotor retardation (Buyukdura et al., 2011). The TMT consists of two parts: TMT-A requires the drawing of lines sequentially to connect 25 encircled numbers distributed on a sheet of paper in ascending order. Task requirements are similar for TMT-B, except that the subject must alternate between numbers and letters (1, A, 2, B, 3, C, and so on). The score for each part represents the amount of time required to complete the task. It was originally designed to test processing speed (TMT-A) or cognitive and attentive flexibility (TMT-B) (Misdraji and Gass, 2010), but it also provides information on visual search, sequencing, and conceptual tracking (Mahurin et al., 2006).

For the TMT, the examiner was instructed to monitor the ongoing progress of the test and to intervene to correct mistakes at the time

Table 2 Clinical and cognitive characteristics of 2048 depressed outpatients at baseline and 6 to 8 weeks after treatment.

	Baseline values			Follow-up values		Statistics		
	N	Average	SD	Average	SD	*t*	df	*p*
QIDS-SR total score	2048	16.10	4.47	7.12	4.95%	60.95	4094	$<10^{-3}$
CGI-S score	2048	4.76	0.76	2.22	0.96	92.82	4094	$<10^{-3}$
RDS score	2002	26.55	8.78	11.37	8.46	55.71	4002	$<10^{-3}$
SDS score	2002	20.25	5.24	10.16	6.71	53.02	4002	$<10^{-3}$
Work/studies		6.67	1.95	3.31	2.54	46.95	4002	$<10^{-3}$
Social life		6.91	1.92	3.56	2.68	45.47	4002	$<10^{-3}$
Family		6.56	1.99	3.29	2.65	44.15	4002	$<10^{-3}$
TMT-A neurocognitive test	1140							
Time (seconds)		63.18	58.44	40.38	36.82	11.14	2278	$<10^{-3}$
Mistakes (number)		0.72	1.57	0.43	3.24	2.72	2278	$<10^{-3}$
TMT-B neurocognitive test	1140							
Time (seconds)		96.88	77.31	66.37	58.77	17.52	2278	$<10^{-3}$
Mistakes (number)		2.16	5.90	1.06	4.79	4.89	2278	$<10^{-3}$
d2 neurocognitive test	508							
GZ (number of marked items)		318.09	173.64	381.07	167.44	5.88	1014	$<10^{-3}$
BR (number of correct marked items)		114.60	72.27	140.91	69.48	5.92	1014	$<10^{-3}$
Kl (correct marked items-incorrect marked items)		105.68	72.67	132.81	71.28	6.01	1014	$<10^{-3}$

CGI-S, Clinical Global Impression Severity; QIDS-SR, Self-Report Quick Inventory of Depressive Symptomatology; RDS, Retardation Depressive Scale; SDS, Sheehan Disability Scale; TMT, Trail Making Test.

of their occurrence, as initially proposed (Hays, 1995). Since timing of the test was not stopped during this intervention, time for correction of errors is included in the total time for completion of the test.

TMT-A and TMT-B ($N=1080$) and d2 ($N=508$) were performed and informative for only one quarter of the sample (24.80%). These patients were comparable to the rest of the sample regarding age ($p=0.128$), gender ($p=0.406$), marital status ($p=0.869$), professional status ($p=0.678$), number of past depressive episodes ($p=0.345$), baseline ($p=0.111$) and post-treatment ($p=0.408$) values of depression severity, RDS psychomotor retardation level ($p=0.273$), and post-treatment values of RDS psychomotor retardation ($p=0.248$). Patients who performed the neurocognitive tests nevertheless had a tendency for more frequent rates of remission (44.91% vs 41.53%, $p=0.062$).

The existence of a practice effect was indirectly assessed in the subgroup of patients with identical QIDS-SR global scores at both visits. In this subgroup of 14 patients, the difference in the values between the two visits did not reach the significance level (TMT-A time [mean $=-0.615$ s; SD=16.993; $p=0.898$], TMT-B time [mean $=-5.182$ s; SD=29.630; $p=0.585$], and the GZ [mean $=+14.667$ signs, SD=140.025, $p=0.775$]), BR [mean $=+6.222$ signs; SD=73.578; $p=0.806$] and KL [mean $=+4.556$ signs, SD=57.133, $p=0.844$] indexes of the d2 test).

2.3. Treatment, follow-up, and data collection

All patients received agomelatine (25–50 mg) once daily at bedtime. Patients were evaluated at the inclusion visit, when their eligibility criteria were verified, data on demographic, clinical, and cognitive variables at baseline documented, and treatment with agomelatine 25 mg initiated. Patients then returned for one follow-up visit between week 6 and week 8, when clinical response was evaluated with a severity rating scale completed by the physician (Clinical Global Impression-Severity [CGI-S] scale) and patient (QIDS-SR), and cognitive tests were again performed.

2.4. Statistical analyses

A graphical appreciation was used to assess the normality of distribution of the factors analyzed (at baseline and the second visit). Q-Q plots were thus performed and showed that dependent variables were close enough to the normal distribution.

A Student's *t*-test was used to determine the difference between continuous variables and Chi-square test in order to compare binary variables. As age, educational level, and professional activity were significantly involved in either the number of past depressive episodes or in cognitive tests (Tables 3 and 4), these items were controlled for when needed (and indicated) as co-variables in quantitative analyses; i.e., partial correlation or analyses of covariance was used controlling for these three factors.

All statistical analyses were carried out using an SPSS 15.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Baseline values of the sample

At inclusion, the majority of the sample was female and on an average 45 years old, with approximately half being married or living with a partner and presently working (Table 1). It was the first episode for 6 out of 10 patients, but for 13.9% it was the third episode or more (Table 1). The baseline severity on the QIDS-SR was around 16, which was in accordance with the clinicians' rating (the CGI-S being quoted as 5 or above [markedly ill] for 70.3% of patients) (Table 2). The average psychomotor retardation (according to the RDS) was 27 (the worst value being 60), and the average social functioning level (assessed by the SDS) was 20 (the worst value being 30). For the neurocognitive tests at baseline, 1 min was required on an average to perform the TMT-A at baseline, with on average only one mistake

Table 3 Clinical and socio-demographic characteristics of patients with baseline psychomotor retardation below or over the media value (27) of the RDS.

		Baseline psychomotor retardation level				Statistics			
		Lowest values (N=1025)			Highest values (N=1023)				
Characteristics		N	Average	SD	N	Average	SD	t	c^2	df	p
Gender	Female	610			635						
	Male	339			387				0.97	1	0.324
Marital status	Single, divorced, or widowed	508			451						
	Married/partner	419			481				7.65	1	0.006
Highest educational level	Below high school	467			595						
	High school and over	439			400				13.10	1	<0.001
Professional activity	Presently working	417			362						
	Retired, unemployed, disability, or sick leave	450			582				17.52	1	<0.001
QIDS-SR			13.87	4.10		18.17	3.66	24.47		1972	<0.001
CGI-S			4.42	0.74		5.14	0.57	24.30		1972	<0.001
SDS			17.96	5.42		21.96	4.08	15.07		1314	<0.001
d2 tests	GZ		354.52	166.92		282.93	171.21	4.70		491	<0.001
	BR		128.31	70.12		101.14	70.78	4.28		491	<0.001
	KL		120.04	72.13		91.44	69.44	4.47		491	<0.001
TMT	TMT-A (time)		55.31	44.79		70.53	67.78	4.18		967	<0.001
	TMT-A (mistakes)		0.59	1.50		0.83	1.62	2.44		1060	0.007
	TMT-B (time)		87.97	67.33		105.14	84.94	3.38		898	<0.001
	TMT-B (mistakes)		1.72	4.18		2.49	7.05	2.09		936	0.018

CGI-S, Clinical Global Impression Severity; QIDS-SR, Self-Report Quick Inventory of Depressive Symptomatology; RDS, Retardation Depressive Scale; SDS, Sheehan Disability Scale; TMT, Trail Making Test.

recorded, while 50% more time was needed for the TMT-B test to be performed, with two mistakes recorded on an average. The results of the d2 test (GZ, BR, and Kl scores) are detailed in Table 2. As expected, the RDS total score correlated highly with all aspects of the d2 and with the speed characteristics of the TMT tests ($p<0.003$), even when controlling for educational level, professional activity, and age ($p<0.004$). Patients with higher (versus lower) clinical level of psychomotor retardation are described in Table 3, splitting the sample in two according to the median value of the RDS (which was 27). Patients with more severe psychomotor retardation at baseline were significantly more frequently single, divorced or widowed (OR=1.29), having an educational level below high school (OR=1.40) and not presently working (OR=1.49). Furthermore, these patients had higher QIDS-SR, SDS and CGI-S scores and had worst performance in all cognitive tests (Table 3).

In testing which factors could influence the results of the neurocognitive tests, we found that (i) age and (ii) presence of a professional activity were involved in the speed at which the TMT-A and TMT-B tests were performed (Table 4). This was not the case, however, for educational level, gender, marital status, and the hour at which the tests were performed. Educational level was the only factor influencing the three aspects of the d2 tests (GZ, BR, and KL). The time at which the test was carried out also impacted the KL value (concentration performance) on the d2 test (Table 4).

3.2. Follow-up values of the sample

Six to eight weeks later, a large improvement was observed on all clinical and cognitive assessments (Table 2), with 67.68% of patients being responders and 43.31% of patients being in remission (N=887). During the observational period, the dose of agomelatine was increased to 50 mg in 17.30% of patients, this group of patients being comparable to the other patients in terms of gender, age, marital status, educational level, and professional activity ($p>0.11$), but also in terms of baseline severity of depression ($p>0.33$) and psychomotor retardation according to clinical or cognitive assessments ($p>0.10$).

At the second visit, there were differences between remitted patients and non-remitted patients regarding several traits (described in Table 5). Apart from having—by definition—less severe clinical symptoms and functional difficulties, patients in remission after treatment were younger, showed a tendency to have had fewer previous depressive episodes, had a lower degree of psychomotor retardation, were quicker on TMT-A and TMT-B, and quoted

Table 4 Influence of socio-demographic and clinical characteristics in two neurocognitive tests at baseline in a sample of 2048 depressed outpatients.

Characteristics		TMT-A		TMT-B		d2 test		
		Speed	Errors	Speed	Errors	GZ	BR	KL
Age	*r*	0.097	0.027	0.129	0.071	−0.052	−0.076	−0.076
	N	882	953	823	852	458	458	458
	p	**0.004**	0.409	**<0.001**	0.038	0.265	0.103	0.265
Gender	*F*	1.610	0.466	0.621	1.459	1.572	0.463	0.394
	df	901	972	841	866	466	466	466
	p	0.205	0.505	0.431	0.227	0.211	0.497	0.530
Professional activity	*F*	7.724	0.741	6.555	2.613	1.354	1.265	0.663
	df	653	703	613	628	346	346	346
	p	**<0.001**	0.477	**0.002**	0.074	0.260	0.284	0.516
Educational level	*F*	0.799	0.013	1.537	2.113	10.060	13.222	10.758
	df	876	945	819	844	455	455	455
	p	0.372	0.908	0.215	0.146	**0.002**	**<0.001**	**0.001**
Marital status	*F*	0.193	0.655	2.089	2.324	0.001	0.140	0.264
	df	885	960	828	856	460	460	460
	p	0.661	0.419	0.149	0.128	0.978	0.708	0.608
Time at which the test was done	*r*	−0.047	0.015	−0.050	−0.028	0.083	0.080	0.094
	N	882	955	826	852	450	450	450
	p	0.160	0.651	0.148	0.415	0.078	0.091	**0.047**
Length of the present episode	r	0.034	0.023	0.018	0.038	0.029	0.078	0.077
	N	895	967	835	862	466	466	466
	p	0.306	0.483	0.597	0.260	0.092	0.092	0.099
Number of episodes	*r*	0.094	0.009	0.137	0.085	−0.133	-0.132	−0.123
	N	896	965	836	861	464	464	464
	p	**0.005**	0.775	**<0.001**	**0.013**	**0.004**	**0.004**	**0.008**

more correct items and less incorrect items in the d2 test (Table 5).

Some patients ($N=876$; 42.77%) were declared by the clinician as having received some form of psychotherapy during the study period. This group of patients was comparable in terms of gender, age, marital status, and professional activity ($p>0.11$) and had equivalent levels of baseline severity according to the QIDS and CGI scale ($p>0.22$) compared with the rest of the sample. Patients who received psychotherapy nevertheless had higher baseline levels of psychomotor retardation according to the RDS ($p<0.001$) and the time needed to carry out the TMT-A (6.89 more seconds; $p=0.026$) and TMT-B (10.45 more seconds; $p=0.016$), with the average number of past depressive episodes also being higher in this group (1.00 compared with 0.84; $p=0.019$).

3.3. The impact of past depressive episodes on retardation

At baseline, the number of past depressive episodes correlated with both the clinical (CGI, QIDS, and RDS) assessments of depression and the neurocognitive tests (speed of the TMT and d2 variables) (Table 6). However, when controlling for age, educational level, and professional activity, only the clinical assessments ($p<0.04$) and the speed at which the TMT tests were carried out ($p<0.003$) significantly correlated with the number of past episodes.

We performed these analyses a second time, focusing on the second set of assessments for the whole group of patients (Table 6). For the neurocognitive tests, the previous analyses were confirmed, showing that the speed on both the TMT and d2 tests is indeed correlated with the number of past depressive episodes (Table 6, Figure 1). But when covariates were included in the analyses, KL and BR values were no longer significantly involved.

We then focused on patients in clinical remission at the second visit, and found no clinical or social features that continued to reflect the number of past episodes; however, the speed on the TMT-A and TMT-B tests and the GZ (quantitative performance) value did continue to reflect this, even when controlling for the three covariates (Table 6).

4. Discussion

In testing whether psychomotor retardation—as assessed by the clinician and through neurocognitive tests—could be a marker of the cumulative burden of past depressive episodes, we found that the speed at which TMT-A and TMT-B were performed was the only assessment that fulfilled the requirements that we set out to test. This was in a relatively large sample of depressed outpatients, before and after treatment. Indeed, the speed at which the TMT tests were carried out correlated with the number of past depressive episodes at baseline, but also after treatment, even when restricting the analyses to patients in

Table 5 Clinical and cognitive characteristics of 2048 outpatients after 6 to 8 weeks of antidepressant treatment, according to the presence (versus the absence) of remission.

Characteristics	Subgroups	In remission (N=885)		Not in remission (N=1161)		Statistics		
		Average or %	SD	Average or %	SD	t or χ^2	df	p
Gender	Female	61.13%		64.68%		2.72	1	0.100
	Male	38.87%		35.32%				
Age		44.72	12.23	45.88	12.29	2.08	1989	0.019
Marital status	Living with a partner	47.17%		46.73%		0.04	1	0.844
	Alone	52.83%		53.27%				
Highest educational level	Below high school	56.53%		54.42%		0.87	1	0.350
	Over high school	43.47%		45.58%				
Professional activity (presently)	Yes	43.13%		45.58%		0.06	1	0.811
	No	56.53%		54.42%				
Length of present episode (weeks)		10.60	36.78	9.36	12.50	0.86	1621	0.196
Number of past episodes		1.45	8.44	1.99	9.33	1.30	1854	0.097
QIDS-SR total score		2.90	1.65	10.33	4.15	55.52	2046	$<10^{-3}$
DSM-IV criteria		6.95	1.10	7.16	1.08	4.19	2046	$<10^{-3}$
CGI-S score		1.82	0.92	3.37	1.20	33.06	2046	$<10^{-3}$
RDS score		5.61	4.79	16.13	8.06	34.42	2009	$<10^{-3}$
SDS score	Work/studies	1.93	1.64	4.58	2.01	27.78	1469	$<10^{-3}$
	Social life	1.86	1.64	4.88	2.16	35.55	2006	$<10^{-3}$
	Family	1.74	1.60	4.72	2.16	35.49	2006	$<10^{-3}$
TMT-A neurocognitive test	Time (seconds)	36.77	32.21	43.42	40.09	2.83	944	0.002
	Mistakes (number)	0.40	4.47	0.46	1.68	0.27	1009	0.391
TMT-B neurocognitive test	Time (seconds)	58.03	48.21	73.66	65.83	4.12	909	$<10^{-3}$
	Mistakes (number)	0.95	6.14	1.16	3.24	0.63	938	0.266
d2 neurocognitive test	GZ (number of marked items)	393.26	166.60	371.24	167.81	1.37	437	0.085
	BR (number of correct marked items)	146.98	69.02	136.01	69.60	1.65	437	0.049
	Kl (correct-incorrect marked items)	140.61	70.41	126.52	71.51	2.07	437	0.019

CGI-S, Clinical Global Impression Severity; QIDS-SR, Self-Report Quick Inventory of Depressive Symptomatology; RDS, Retardation Depressive Scale; SDS, Sheehan Disability Scale; TMT, Trail Making Test.

remission. Furthermore, even though certain confounders were detected that partly explained the speed at which the TMT was performed, controlling for these did not reduce the strength of the observed correlation.

If such results are confirmed in an independent sample, and especially if neurocognitive assessments are performed at a greater distance from remission, the present finding could be considered an important step towards understanding why and how, with more past depressive episodes, there exists a higher degree of remaining symptoms (Judd, 2012), poorer functional remission (Sarapas et al., 2013) and higher risk of later relapses (Solomon et al., 1997). It could also shed light on the fact that patients with residual depressive symptoms have an increased risk of relapse compared to those patients in full remission (Cornwall and Scott, 1997; Paykel et al., 1995), as residual depressive symptoms might also reflect psychomotor retardation.

The results of our study also stress for the first time that distinguishing between the neurocognitive and clinical aspects of psychomotor retardation is fruitful, potentially not only for research into the mechanisms involved in the recurrence of major depressive disorder, but also for ensuring more adequate treatment approaches for prevention strategies.

In our study, TMT-A and TMT-B appeared to more directly reveal the impact of past depressive episodes—whatever the time point of the assessment—than the different aspects of the d2 test. Furthermore, the simple TMT-A (drawing a line between numbers increasing in value) performed equally well as the more demanding TMT-B (which requires set shifting). Accordingly, the value from the d2 test that performed best was GZ (Table 6), which consists of the number of total signs marked, even if they are not appropriate. These three results could plead in favor of a specific role for speed, rather than accuracy and complexity, and thus psychomotor retardation.

One potential explanation for this result is that the aspects of psychomotor retardation involved in such scar

Table 6 Correlation between the number of past depressive episodes and demographic, clinical, and cognitive characteristics of depressed outpatients, at baseline and after treatment (for all patients, and those in remission).

Variables	At baseline ($N=1856$)				After treatment						
					Whole sample ($N=1856$)			Remitted patients ($N=475$)			
	F	r	p	p'	r	p	p'	F	r	p	p'
Age		0.244	<0.001						0.209	<0.001	
Gender	0.311		0.577					2.612		0.107	
Professional activity	0.247		0.117					2.564		0.078	
Marital status	1.351		0.245					0.302		0.583	
Educational level	21.211		<0.001					10.736		0.001	
Psychomotor retardation (RDS)		0.099	<0.0010	0.007	0.117	<0.0010	0.068		0.033	0.488	0.150
CGI-S		0.124	<0.001	0.0060	0.099	<0.001	0.068		−0.011	0.816	0.186
QIDS-SR		0.0780	0.001	0.039	0.129	<0.001	0.007		0.012	0.788	0.526
SDS		0.048	0.093	0.086	0.099	<0.001	0.048		−0.044	0.406	0.186
TMT-A (errors)		−0.009	0.775	0.710	−0.117	0.610	0.384		−0.036	0.536	0.449
TMT-A (speed)		0.094	0.005	0.002	0.129	<0.001	0.002		0.292	<0.001	<0.001
TMT-B (errors)		0.085	0.013	0.905	−0.112	0.722	0.321		−0.039	0.512	0.505
TMT-B (speed)		0.137	0.004	0.001	0.166	<0.001	<0.001		0.214	<0.001	<0.001
GZ (d2 test)		−0.133	0.004	0.125	−0.200	<0.001	0.006		−0.221	0.021	0.009
Kl (d2 test)		−0.123	0.008	0.163	−0.125	0.013	0.172		−0.148	0.122	0.139
BR (d2 test)		−0.132	0.004	0.136	−0.141	0.005	0.158		−0.157	0.103	0.087

p': the p-Value controlling for 'age', 'educational level' and 'professional activity'.
CGI-S, Clinical Global Impression Severity; QIDS-SR, Self-Report Quick Inventory of Depressive Symptomatology; RDS, Retardation Depressive Scale; SDS, Sheehan Disability Scale; TMT, Trail Making Test.

effects, are: (i) *above attention* (which is a prerequisite to test speed); (ii) *below cognitive flexibility or executive dysfunction* (which is more demanding, and potentially more contaminated by depressive symptoms); and (iii) *different to the usual clinical assessments* as captured by the RDS (potentially because of the overlap with the severity of the depressive episode). The nature of executive dysfunction in depression has not been fully clarified. Although psychomotor slowing is well documented in mood disorder (e.g., Austin et al., 2001), and is one of the diagnostic criteria for the disorder, other cognitive impairments in mood disorder include deficits in attention control, working memory, and processing speed (Elderkin-Thompson et al., 2004). These information-processing deficits can, in turn, affect performance on other cognitive processes, including executive function (*for a general discussion, see* Robbins et al., 1998).

Cognitive speed might be more specifically involved, as a previous study of depression and cognition in multiple sclerosis concluded that the patients with depression were mainly characterized by slow information processing speed, whereas executive functioning was unaffected (Arnett et al., 1994). In younger patients with moderate depression, no impairment was reported in working memory whereas a significant decrease in motor speed and attention set-shifting (Purcell et al., 1997) was observed, with those with overall greater illness severity (higher rate of admission for treatment of depression) being more impaired on the set-shifting task. In searching for a relevant phenotype in mood disorder, one study detected that patients with the highest score on psychomotor retardation testing were also the ones with a longer duration of illness, an earlier age of onset, and more depressive episodes, which is clearly in accordance with our own results (Calugi et al., 2011). Interestingly, psychomotor retardation was a predictor of delayed response to treatment with either interpersonal psychotherapy or selective serotonin reuptake inhibitor pharmacotherapy (Frank et al., 2011).

Psychomotor retardation might, therefore, capture the negative impact of past depressive episodes in accordance with Widlocher's description (1983). Widlocher proposed that psychomotor retardation (including both observed motor behavior and inferred mental functions) is a 'primary disturbance' in affective disorders. Aside from the present study, this view is also supported by positive research showing stable cognitive abnormalities after remission (Paradiso et al., 1997; Kessing, 1998), and a correlation between lifetime depression and: (i) a composite score of cognitive impairment (Kessing, 1998; Hasselbalch et al., 2013); (ii) response latencies using computerized tests such as CANTAB (Beats et al., 1996); (iii) executive functions requiring planning and problem solving (Bhardwaj et al., 2010); (iv) longer time to perform tests requiring attention and executive functions (Paelecke-Habermann et al., 2005); and even (v) TMT-A and TMT-B performance (relying on number of hospitalizations rather than on number of depressive episodes) (Preiss et al., 2009). Psychomotor retardation has also been assessed on a more clinical basis through the use of a lifetime psychomotor retardation (LPR) factor, which showed that compared with patients with low scores, high LPR scorers had more past depressive episodes (Calugi et al., 2011).

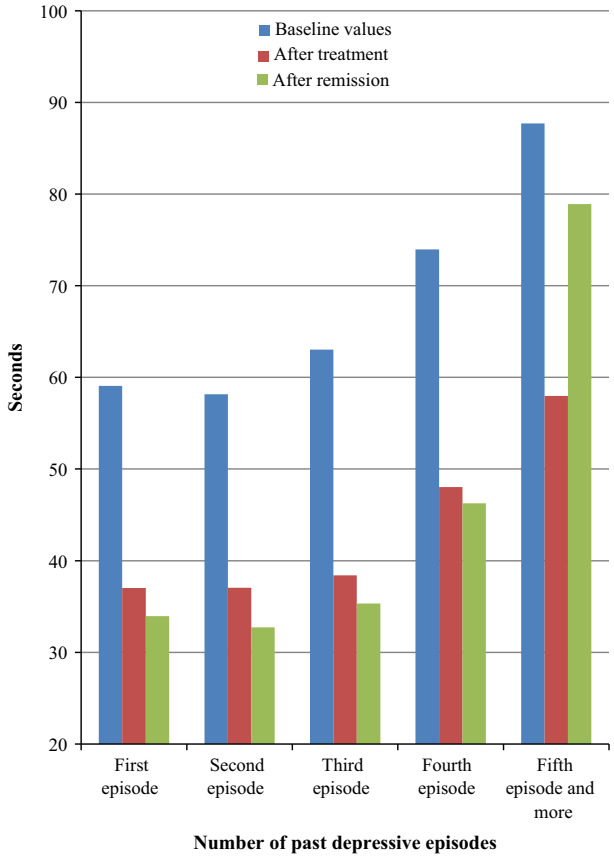

Figure 1 TMT-A performance (speed) according to the number of past depressive episodes.
The time needed to perform Trail Making Test A (TMT-A) increases with the number of past depressive episodes, both when carried out at baseline (blue boxes) and when carried out after treatment on the whole sample (red boxes) and when limited to patients in remission (green boxes). See Table 4 for corresponding correlations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Also, interestingly, in a sample of 25 bipolar patients who were euthymic for 3 months, the result of the TMT-B test correlated with the cumulative duration of past depressive episodes, but not of manic episodes (Van Gorp et al., 1998). Cognitive impairment in MDD has been associated with higher rates of relapse and recurrence (Majer et al., 2004; Sumner et al., 2010), reinforcing the idea that neurocognitive abnormalities could constitute markers of acquired vulnerability. Nevertheless, not all studies have confirmed the hypothesis of a direct link between past depressive episodes and cognitive abnormalities (for review see Hasselbalch et al., 2013). This is in fact to be expected if one considers the weight of past episodes on neurocognitive abnormalities, which is regularly quoted in these studies as being of medium to small range, and thus requires large samples to be detected. Indeed, these negative studies have had more limited statistical power, as the number of patients has been below 30. Another source of heterogeneity in the results arises from the fact that the studies have investigated various aspects of neurocognitive deficits that might not systematically overlap.

Different limitations in our work should be pointed out. First, not all patients received the neurocognitive tests, therefore it is expected that bias would have occurred in those patients who were recruited with higher levels of cooperativeness and who were potentially less depressed. However, the clinical characteristics of the patients who carried out the tests were largely comparable with the rest of the sample (see Section 2). Another limitation of our sample is the requirement of no associated medication, antipsychotic, mood stabilizer, or benzodiazepine. Although this was needed to obtain valid neurocognitive test results, it is possible that severely depressed anxious patients needing co-prescription were less frequently recruited in this non-interventional study. On the other hand, the sample tested in this study had a large degree of variability in terms of severity and past number of episodes, which were the only prerequisites for inclusion. In line with this, the SD of the delay between the two visits was relatively large (SD=11). In accordance with the fact that this was a non-interventional study, we proposed a relatively large time lag before the second visit to facilitate inclusion. This potential issue may in fact have had limited impact, as the lag was not associated with any clinical or cognitive characteristics of patients at the second visit.

Another potential limitation is that, although we assessed three aspects of psychomotor retardation through neurocognitive tests and a specific clinical assessment, it is difficult to predict if our results would be replicated if relying on other important aspects of psychomotor retardation, more clearly distinguishing motor from cognitive aspects of neurocognitive retardation, such as the ones related to movement and speech. Examples would be speed and paucity of movement and walk, objective latencies, pauses, lack of reactivity, difficulty of initiation, and speed of speech. The third limitation relates to the fact that all patients in the study received treatment, and with a single drug, with neither placebo nor comparator. With no comparator, it is difficult to detect if the cognitive improvement with agomelatine is a specific effect, and with no placebo, it is difficult to know if the same results at remission would be found with no antidepressive treatment.

The presence of another axis I DSM-IV diagnosis and non-antidepressant psychotropic treatments constituted exclusion criteria. It is nevertheless difficult to rule out the presence of comorbidity in our sample (such as bipolar disorder or generalized anxiety disorders), especially as no structured interview was performed at baseline. This problem could have consequences. For example, bipolar disorder patients with a mixed depression have lower retardation level according to one study (Sani et al., 2014) and a significant correlation ($r>0.4$) has been detected between anxiety and psychomotor retardation in depressed patients (Goekoop et al., 2006). It is therefore important to state that, even if our findings were detected in depressed patients, specifically attributing our results to non-comorbid major depressive disorder would require a structured interview encompassing potentially associated bipolar and anxiety disorders.

Last, a practice effect is always difficult to control for when performing neurocognitive tests at least twice, and may partly explain the improvement observed at the second visit. Indirect evidence might plead against a major role for

this bias, as in restricting the analyses to all ($N=14$) patients who had exactly the same QIDS value at the two visits (and were therefore not influenced by the expected decrease in depressive symptoms), we did not find a significant improvement. Taken together, these results might plead in favor of a scar effect of past depressive episodes, although long-term studies conducted at a distance from any depressive episode would be the most adequate way to reach any conclusion.

If it can be prospectively confirmed that past depressive episodes have a negative cumulative impact on psychomotor retardation, intervention might be proposed for at-risk individuals, mainly in the early stages of depressive disorder. First-episode disorders might indeed be more sensitive to care, especially as psychotherapy early in life and at early stages of illness might reduce the rate of recurrence of depressive episodes (Clarke et al., 1999; Jarrett et al., 2001) and as the development of psychotropic drugs now involves neurocognition (Millan et al., 2012).

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Contributors

GP and BF designed the study and wrote the protocol. GP and CMML undertook the statistical analyses. CMML managed the literature searches, and GP wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Over the past 5 years, Philip Gorwood has received research grants from Eli Lilly and Servier, and fees for presentations at congresses or participation in scientific boards from AstraZeneca, Bristol-Myers-Squibb, Janssen, Lilly, Lundbeck, Otsuka, Roche, and Servier.

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